UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,439	10/22/2003	David J. Pinsky	51917-CB-PCT-US/JPW/AJM/A	8415

7590 11/17/2006

John P. White, Esq.
cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,439	PINSKY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/04, 9/20/04, 1/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment received August 25, 2006 is acknowledged.

Claims 1-24 and 26-32 have been canceled.

Claims 25 and 33-35 are pending in the instant application.

Applicant's election with traverse of Group VI, claims 25 and 33-35, as these claims read on methods of treating reperfusion injury by administering Factor IXa compounds which are polypeptides in the reply filed on 25 August 206 is acknowledged. The traversal is on the ground that there is no search burden in examining all currently recited methods. This is not found persuasive because as was stated in the restriction requirement mailed 7/25/06, applicant has recited multiple methods that rely upon the administration of patentably distinct products that dependent from generic linking claims. The products used in the methods are patentably distinct since art that anticipates or renders obvious one product would not necessarily anticipate or render obvious the other products since the structures and mechanism of action of the products are diverse, and as such methods utilizing said products would also not be anticipated and/or rendered obvious.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25 and 33-35 are under examination as they read on methods of treating reperfusion injury by administering polypeptides that are Factor IXa compounds.

Specification

2. Applicant's amendments to the specification have been noted and objected. Applicant has amended the first line of the specification as part of the preliminary amendments filed 10/22/03 to claim priority to U.S. serial number 09/053,871. Claims for priority to non-provisional applications must indicate the relationship between the applications (i.e. continuation, divisional, continuation-in-part). No information concerning the relationship of the '871 application to the other applications have been

provided. As such, applicant's benefit claim is noted but has not been fully entered, thus the objection to the specification. It appears that the '871 application is related to PCT/US99/07175 as a continuation-in-part and that the '871 application appears to support the instant invention as currently recited. As such the instant claims have been accorded the date of April 1, 1998 for examination purposes in relation to the prior art.

Applicant should make appropriate amendments to the first line of the specification such that applicant's benefit claim can be properly recorded.

Information Disclosure Statement

3. Applicant's IDS forms received 6/18/04, 9/20/04 and 1/3/05 are acknowledged and have been considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 25 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for treating reperfusion injury in a subject by administering a "Factor IXa compound" to the subject.

There is not sufficient direction or guidance provided by the specification to assist one skilled in the art in the selection of any "Factor IXa compound" that is effective for treating all reperfusion injuries, nor is there sufficient evidence provided that all such compounds are effective for treating all reperfusion injuries, especially in view of the broad definition of "Factor IXa compound" disclosed in the specification. The

specification discloses that "a factor IXa compound means a compound which inhibits or reduces the conversion of Factor X to factor Xa by naturally occurring Factor IXa" and that such compounds comprise, but are not limited to, chemical modifications of Factor IXa, any recombinant mutated form of Factor IXa, nucleic acids, anti-Factor IXa antibodies or fragments thereof, saccharides, ribozymes, small organic molecules or peptidomimetics (see the paragraph spanning pages 20 and 21). It would require undue experimentation to produce all such possible "Factor IXa compounds" and identify which of said compounds can be used to treat reperfusion injury due to their ability to inhibit Factor Xa generation, thus inhibiting thrombin generation and ultimately inhibiting coagulation. As such the scope of the claimed invention is not commensurate with the enablement provided in the disclosure.

It is known in the art that the amino acid sequence of a protein determines its structural and functional properties, and that maintenance of structure and function relationships cannot be predicted by amino acid sequence analysis. Skolnick et al. (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein based upon amino acid sequence analysis is inaccurate, in part because of the multifunctional nature of proteins (see particularly the Abstract and the section titled Sequence-based approaches to function prediction on page 34). Even in situations where there is some confidence of a similar overall structure between two sequences, only experimental research can confirm the artisan's best guess as to the function of the structurally related sequence (see in particular the Abstract and Box 2 on page 36). The complexity and unpredictability of the problem of assigning function based on amino acid sequence analysis rises as the percent similarity or identity falls (see Whisstock et al., Quarterly Reviews of Biophysics, 2003, 36:307-340, particularly the sentence that spans pages 321 and 323).

In the case of Factor IXa, it is known that even minor structural differences that arise due to amino acid substitutions at one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis (Brandstetter et al.,

of record on the 1/3/05 IDS). The genus of "Factor IXa compounds" is not limited to polypeptides that differ in sequence from native Factor IXa and comprises a wide spectrum of diverse molecules that differ in structure and the biophysical mechanistic pathways by which they inhibit the ability of Factor IX to convert Factor X to Factor Xa. The structure required of "Factor IXa compound" to comprise the recited property does not appear to be disclosed. No working examples appear to have been provided concerning "Factor IXa compounds" other than Factor IXa that has been chemically inactivated with dansyl-glu-gly-arg-choromethylketone (see particularly lines 30-36 of page 59).

Therefore, given the breath of the compounds recited in the instant claimed methods, the lack of sufficient guidance and working examples in the specification, the unpredictability of maintenance of protein function in light of changes to the primary amino acid sequence and the differing pathways by which "factor IXa compounds" inhibit the production of Factor Xa, a skilled artisan would be required to engage in undue trial and error research to make and use "factor IXa compounds" in the instant claimed methods.

6. Claims 25 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed methods of treating reperfusion injury by administering a "Factor IXa compound" to a patient. The specification states "a factor IXa compound means a compound which inhibits or reduces the conversion of Factor X to factor Xa by naturally occurring Factor IXa" (see the sentence spanning pages 20 and 21). Non-limiting examples of such compounds comprise peptides, peptidomimetics, nucleic acids, small molecules, mutated peptides or nucleic acids, muteins, antibodies and antibody fragments, saccharides and ribozymes (see particularly lines 26-30 of page 18 and the paragraph spanning pages 20 and 21), and the specification comprises an

example wherein Factor IXa was chemically inactivated with dansyl-glu-gly-arg-choromethylketone (see particularly lines 30-36 of page 59).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court stated:

"A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant has recited methods that utilize a genus of molecules that have a common function, but the specification does not appear to teach a core structure that is common to all "Factor IXa compounds" or what structure or structures give rise to the disclosed function of "Factor IXa compounds". Further, the structure of the chemically inactivated Factor IX polypeptide disclosed in the examples does not appear to be a representative structure for the genus of "Factor IXa compounds".

Therefore, it appears that the broad genus of "Factor IXa compounds" recited by applicant for use in the instant methods lacks adequate written description because there does not appear to be any correlation between the structure and function for this genus of compounds. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of "Factor IXa polypeptides" at the time the instant invention was filed

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 25 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toledo-Pereya (Klin Wochenschr, 1991, 69:1099-1104) in view of Benedict et al. (of record on the 9/20/04 IDS) and in view of King (US Patent 5,589,571).

Toledo-Pereyra taught that at the time the instant invention was made, a skilled artisan knew that "reperfusion injury" was often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further taught that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion injury that needs to be treated with pharmacological agents such as heparin to inhibit coagulation (see particularly the right column of page 1099, Table 7, and the right column of page 1103). These teachings differ from the instant claimed invention in that Toledo-Pereyra does not disclose the administration of "Factor IXa compounds" to treat thrombosis in reperfusion injury.

Benedict et al. taught that inactivated Factor IXa was successfully used to inhibit thrombus formation in vivo (see entire document, particularly the abstract). Benedict et al. further teach that administration of inactivated factor IXa offers an advantage over the administration of heparin for inhibiting coagulation in that animals treated with heparin suffered from excessive bleeding while animals given inactivated Factor IXa did not manifest excessive bleeding (see particularly figure 4).

King taught the manufacture of inactivated blood factors using recombinant means, such blood factors including inhibited Factor IXa, that offer the advantages of high purity and high yield (see entire document, particularly lines 1-30 of column 5, lines 26-30 of column 6, and lines 3-11 of column 2).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer inactivated recombinant Factor IXa to patients to treat reperfusion injury. Motivation to do so at the time the invention was made comes from the teachings of Toledo-Pereyra that thrombus formation in reperfusion injury is to be treated with heparin and the teachings of Benedict et al. that inactivated Factor IXa is better than heparin at inhibiting thrombus formation in vivo because unlike heparin, inactivated factor IXa administration does not lead to excessive

bleeding. A skilled artisan would be further motivated to use a recombinant form of inactivated Factor IXa since such compounds can be made with high purity and high yield as taught by King et al. Note that synthetic molecules can be made recombinantly.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 25 and 33-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,316,403 in view of Toledo-Pereya (Klin Wochenschr, 1991, 69:1099-1104) and in view of King (US Patent 5,589,571).

The claims of the '403 patent recite methods of treating ischemic disorders by administering inactivated factor IX to a patient to inhibit coagulation so as to treat the ischemic disorder in the patient. Note that dependent claims in the '403 patent recite that factor IX is inactivated at it active site, and that the compounds administered in the '403 patent claims are a species of the genus of "Factor IXa compounds" since they "inhibit or reduce the conversion of Factor X to Factor Xa by naturally occurring Factor

IX" as per the definition of this term in the instant specification (see particularly from line 37 of page 20 to line 20 of page 22). The claims of the '403 patent differ from the instant claimed invention in that the claims of the '403 patent do not specifically recite reperfusion injury and do not recite that the inactivated Factor IX is made recombinantly.

Toledo-Pereyra teaches that at the time of the instant invention, a skilled artisan would know that "reperfusion injury" is often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). Toledo-Pereyra further teaches that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion (see particularly the right column of page 1099 and Table 7 on page 1103).

King teaches the manufacture of inactivated blood factors using recombinant means, such blood factors including inhibited Factor IXa, that offer the advantages of high purity and high yield (see entire document, particularly lines 1-30 of column 5, lines 26-30 of column 6, and lines 3-11 of column 2).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer factor IXa compounds, such as inactivated factor IX and IXa to treat reperfusion injuries. Motivation to do so comes from the teachings of the '403 patent which teaches that "Factor IXa" compounds are to be administered to inhibit thrombosis in a patient, and the teachings of Toledo-Pereyra that thrombosis is an important pathophysiological even that occurs in reperfusion injury. A person of skill in the art would be motivated to use a recombinant "Factor IXa" compound in such methods because such compounds can be readily obtained in high purity and high yield using the methods and teachings of King.

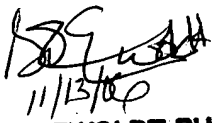
11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
November 8, 2006



11/13/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER